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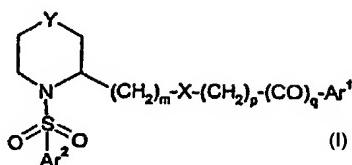
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(54) Title: NOVEL COMPOUNDS



(57) Abstract: This invention relates to N-aryl sulphonyl cyclic amine derivatives of formula (I); and their use as orexin antagonists.

Novel Compounds

This invention relates to *N*-aryl sulphonyl cyclic amine derivatives and their use as pharmaceuticals.

- 5 Many medically significant biological processes are mediated by proteins participating in signal transduction pathways that involve G-proteins and/or second messengers.
- 10 Polypeptides and polynucleotides encoding the human 7-transmembrane G-protein coupled neuropeptide receptor, orexin-1 (HFGAN72), have been identified and are disclosed in EP-A-875565, EP-A-875566 and WO 96/34877. Polypeptides and polynucleotides encoding a second human orexin receptor, orexin-2 (HFGANP), have been identified and are disclosed in EP-A-893498.
- 15 Polypeptides and polynucleotides encoding polypeptides which are ligands for the orexin-1 receptor, e.g. orexin-A (Lig72A) are disclosed in EP-A-849361.
- 20 Orexin receptors are found in the mammalian host and may be responsible for many biological functions, including pathologies including, but not limited to, depression; anxiety; addictions; obsessive compulsive disorder; affective neurosis/disorder; depressive neurosis/disorder; anxiety neurosis; dysthymic disorder; behaviour disorder; mood disorder; sexual dysfunction; psychosexual dysfunction; sex disorder; sexual disorder; schizophrenia; manic depression; delerium; dementia; severe mental retardation and dyskinesias such as Huntington's disease and Gilles de la Tourett's syndrome; disturbed biological and circadian rhythms; feeding disorders, such as anorexia, bulimia, cachexia, and obesity; diabetes; appetite/taste disorders; vomiting/nausea; asthma; cancer; Parkinson's disease; Cushing's syndrome / disease; basophil adenoma; prolactinoma; hyperprolactinemia; hypopituitarism; 25 hypophysis tumor / adenoma; hypothalamic diseases; Froehlich's syndrome; adrenohypophysis disease; hypophysis disease; hypophysis tumor / adenoma; pituitary growth hormone; adrenohypophysis hypofunction; adrenohypophysis hyperfunction; hypothalamic hypogonadism; Kallman's syndrome (anosmia, hyposmia); functional or psychogenic amenorrhea; hypopituitarism; hypothalamic hypothyroidism; hypothalamic- 30 adrenal dysfunction; idiopathic hyperprolactinemia; hypothalamic disorders of growth hormone deficiency; idiopathic growth hormone deficiency; dwarfism; gigantism; acromegaly; disturbed biological and circadian rhythms; and sleep disturbances associated with such diseases as neurological disorders, neuropathic pain and restless leg syndrome, heart and lung diseases; acute and congestive heart failure; hypotension; hypertension; 35 urinary retention; osteoporosis; angina pectoris; myocardial infarction; ischaemic or haemorrhagic stroke; subarachnoid haemorrhage; head injury such as sub-arachnoid haemorrhage associated with traumatic head injury; ulcers; allergies; benign prostatic hypertrophy; chronic renal failure; renal disease; impaired glucose tolerance; migraine; hyperalgesia; pain; enhanced or exaggerated sensitivity to pain, such as hyperalgesia, 40 causalgia and allodynia; acute pain; burn pain; atypical facial pain; neuropathic pain; back pain; complex regional pain syndromes I and II; arthritic pain; sports injury pain; pain related to infection, e.g. HIV, post-polio syndrome, and post-herpetic neuralgia; phantom limb pain; labour pain; cancer pain; post-chemotherapy pain; post-stroke pain; post-

operative pain; neuralgia; nausea and vomiting; conditions associated with visceral pain including irritable bowel syndrome, migraine and angina; urinary bladder incontinence e.g. urge incontinence; tolerance to narcotics or withdrawal from narcotics; sleep disorders; sleep apnea; narcolepsy; insomnia; parasomnia; jet-lag syndrome; and neurodegenerative 5 disorders, which includes nosological entities such as disinhibition-dementia-parkinsonism-amyotrophy complex; pallido-ponto-nigral degeneration, epilepsy, and seizure disorders.

Experiments have shown that central administration of the ligand orexin-A (described in more detail below) stimulated food intake in freely-feeding rats during a 4 hour time period. This increase was approximately four-fold over control rats receiving 10 vehicle. These data suggest that orexin-A may be an endogenous regulator of appetite. Therefore, antagonists of its receptor may be useful in the treatment of obesity and diabetes, see *Cell*, 1998, 92, 573-585.

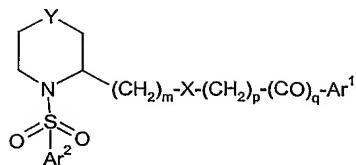
There is a significant incidence of obesity in westernised societies. According to WHO definitions a mean of 35% of subjects in 39 studies were overweight and a further 15 22% clinically obese. It has been estimated that 5.7% of all healthcare costs in the USA are a consequence of obesity. About 85% of Type 2 diabetics are obese, and diet and exercise are of value in all diabetics. The incidence of diagnosed diabetes in westernised countries is typically 5% and there are estimated to be an equal number undiagnosed. The incidence of both diseases is rising, demonstrating the inadequacy of current treatments which may be 20 either ineffective or have toxicity risks including cardiovascular effects. Treatment of diabetes with sulphonylureas or insulin can cause hypoglycaemia, whilst metformin causes GI side-effects. No drug treatment for Type 2 diabetes has been shown to reduce the long-term complications of the disease. Insulin sensitizers will be useful for many diabetics, however they do not have an anti-obesity effect.

25 Rat sleep/EEG studies have also shown that central administration of orexin-A, an agonist of the orexin receptors, causes a dose-related increase in arousal, largely at the expense of a reduction in paradoxical sleep and slow wave sleep 2, when administered at the onset of the normal sleep period. Therefore antagonists of its receptor may be useful in the treatment of sleep disorders including insomnia.

30 The present invention provides *N*-aryl sulphonyl cyclic amine derivatives which are non-peptide antagonists of human orexin receptors, in particular orexin-1 receptors. In particular, these compounds are of potential use in the treatment of obesity, including obesity observed in Type 2 (non-insulin-dependent) diabetes patients, and/or sleep disorders. Additionally these compounds are useful in the treatment of stroke, particularly 35 ischemic or haemorrhagic stroke, and/or blocking the emetic response, i.e. useful in the treatment of nausea and vomiting.

International Patent Applications WO99/09024, WO99/58533, WO00/47577 and WO00/47580 disclose phenyl urea derivatives and WO00/47576 discloses quinolinyl cinnamide derivatives as orexin receptor antagonists. WO01/96302 discloses *N*-aroyl cyclic 40 amine derivatives.

According to the invention there is provided a compound of formula (I):



(I)

wherein:

Y represents a bond, oxygen, NQ or a group $(\text{CH}_2)_n$, wherein n represents 1, 2 or 3;

5 m represents 1, 2, or 3;

p represents 0 or 1;

q represents 0 or 1 provided that when q = 1, p = 0;

X is NR, wherein R is H or $(\text{C}_{1-4})\text{alkyl}$;

Q is H or $(\text{C}_{1-4})\text{alkyl}$;

10 Ar^1 is aryl, or a mono or bicyclic heteroaryl group containing up to 4 heteroatoms selected from N, O and S; any of which may be optionally substituted;

Ar^2 represents phenyl or a 5- or 6-membered heterocyclyl group containing up to 3 heteroatoms selected from N, O and S, wherein the phenyl or heterocyclyl group is substituted by R^1 and further optional substituents; or Ar^2 represents an optionally

15 substituted bicyclic aromatic or bicyclic heteroaromatic group containing up to 4 heteroatoms selected from N, O and S;

R^1 represents hydrogen, optionally substituted $(\text{C}_{1-4})\text{alkoxy}$, halo, cyano, optionally substituted $(\text{C}_{1-6})\text{alkyl}$, optionally substituted phenyl, or an optionally substituted 5- or 6-membered heterocyclic ring containing up to 4 heteroatoms selected from N, O and S;

20 or a pharmaceutically acceptable salt thereof.

Preferably m is 1 when p is 0.

In a further preferred embodiment X is NH; m is 1 and p is 0.

Examples of when Ar^1 is a mono or bicyclic heteroaryl are quinoxaliny

25 quinazolinyl, pyridopyrazinyl, benzoxazolyl, benzothiophenyl, benzimidazolyl, naphthyridinyl, pyridinyl, pyrimidinyl, thiazolyl, pyridazinyl, pyrazinyl, oxazolyl, triazolyl, imidazolyl, pyrazolyl, quinolinyl, benzofuranyl, indolyl, benzothiazolyl, oxazolyl[4,5-b]pyridiyl, pyridopyrimidinyl, isoquinolinyl, furanyl or thienyl.

Preferably Ar^1 is benzofuranyl, quinoxaliny, pyridinyl or pyrimidinyl.

30 When Ar^2 is a 5- or 6-membered heterocyclyl group containing up to 3 heteroatoms selected from N, O and S, it may be furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, pyridyl, triazolyl, triazinyl, pyridazinyl, pyrimidinyl, isothiazolyl, isoxazolyl, pyrazinyl or pyrazolyl.

When Ar^2 is an optionally substituted bicyclic aromatic or bicyclic heteroaromatic it 35 is selected from benzofuryl, benzimidazolyl, quinolinyl, quinoxaliny, naphthyl, benzotriazolyl, benzothienyl, benzoxazolyl, naphthyridinyl, isoquinolinyl, quinazolinyl, indolyl, benzothiazolyl, or benzothiadiazolyl.

Preferably Ar² represents optionally substituted phenyl, pyridyl, thiazolyl, pyrazolyl, benzofuryl, naphthyl, triazolyl, quinoxaliny, quinolinyl, isoquinolinyl, benzimidazolyl, benzothienyl, benzotriazolyl, benzothiazolyl, indolyl or thieryl.

Most preferably Ar² represents optionally substituted phenyl or napthyl.

5 When R¹ is a 5- or 6-membered heterocyclyl group containing up to 4 heteroatoms selected from N, O and S, it may be furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, pyridyl, triazolyl, triazinyl, pyridazinyl, pyrimidinyl, isothiazolyl, isoxazolyl, pyrazinyl, pyrazolyl, tetrazoyl, piperazinyl, piperidinyl, morpholinyl or thiomorpholinyl.

10 Alternatively R¹ is selected from optionally substituted(C₁₋₄)alkoxy, halo, cyano, optionally substituted(C₁₋₆)alkyl or optionally substituted phenyl.

Preferably R¹ is optionally substituted (C₁₋₄)alkoxy, halo, optionally substituted(C₁₋₆)alkyl or optionally substituted phenyl.

15 More preferably R¹ is trifluoromethoxy, trifluoromethyl, methoxy, (C₁)alkyl, chloro, or optionally substituted phenyl.

Optional substituents for the groups Ar¹, Ar², R and R¹ include halogen, hydroxy, oxo, cyano, nitro, (C₁₋₄)alkyl, (C₁₋₄)alkoxy, hydroxy(C₁₋₄)alkyl, hydroxy(C₁₋₄)alkoxy, halo(C₁₋₄)alkyl, halo(C₁₋₄)alkoxy, aryl(C₁₋₄)alkoxy, (C₁₋₄)alkylthio, hydroxy(C₁₋₄)alkyl, (C₁₋₄)alkoxy(C₁₋₄)alkyl, (C₃₋₆)cycloalkyl(C₁₋₄)alkoxy, (C₁₋₄)alkanoyl, (C₁₋₄)alkoxycarbonyl, (C₁₋₄)alkylsulfonyl, (C₁₋₄)alkylsulfonyloxy, (C₁₋₄)alkylsulfonyl(C₁₋₄)alkyl, arylsulfonyl,

arylsulfonyloxy, arylsulfonyl(C₁₋₄)alkyl, (C₁₋₄)alkylsulfonamido, (C₁₋₄)alkylamido, (C₁₋₄)alkylsulfonamido(C₁₋₄)alkyl, (C₁₋₄)alkylamido(C₁₋₄)alkyl, arylsulfonamido, arylcarboxamido, arylsulfonamido(C₁₋₄)alkyl, arylcarboxamido(C₁₋₄)alkyl, aroyl, aroyl(C₁₋₄)alkyl, or aryl(C₁₋₄)alkanoyl group; a group R^aR^bN-, R^aOCO(CH₂)_r, R^aCON(R^a)(CH₂)_r,

25 R^aR^bNCO(CH₂)_r, R^aR^bNSO₂(CH₂)_r or R^aSO₂NR^b(CH₂)_r where each of R^a and R^b independently represents a hydrogen atom or a (C₁₋₄)alkyl group or where appropriate R^aR^b forms part of a (C₃₋₆)azacycloalkane or (C₃₋₆)(2-oxo)azacycloalkane ring and r represents zero or an integer from 1 to 4. Additional substituents are (C₁₋₄)acyl, aryl, aryl(C₁₋₄)alkyl, (C₁₋₄)alkylamino(C₁₋₄)alkyl, R^aR^bN(CH₂)n-, R^aR^bN(CH₂)nO-, wherein n represents an integer from 1 to 4. Additionally when the substituent is R^aR^bN(CH₂)n- or R^aR^bN(CH₂)nO,

30 R^a with at least one CH₂ of the (CH₂)n portion of the group form a (C₃₋₆)azacycloalkane and R^b represents hydrogen, a (C₁₋₄)alkyl group or with the nitrogen to which it is attached forms a second (C₃₋₆)azacycloalkane fused to the first (C₃₋₆)azacycloalkane.

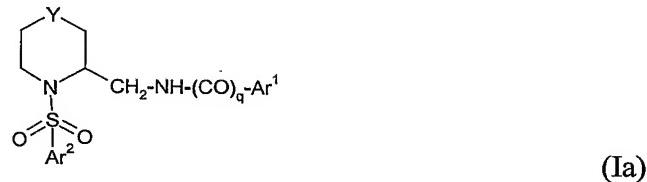
Preferred optional substituents for Ar² are halogen, cyano, (C₁₋₄)alkyl and (C₁₋₄)alkoxy.

Preferred optional substituents for Ar¹ are halogen and cyano.

Preferred optional substituents for R¹ are halogen, (C₁₋₄)alkoxy and (C₁₋₄)alkyl.

In the groups Ar¹ and Ar², substituents positioned *ortho* to one another may be linked to form a ring.

Illustrative compounds of formula (I) are selected from compounds having a core structure (Ia)



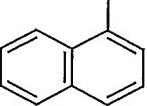
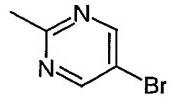
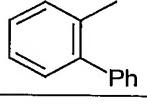
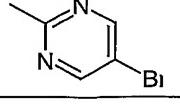
5

and having Y, q, Ar¹ and Ar² as shown in table1:

Table 1

Example	Y	q	Ar ²	Ar ¹
1	CH ₂	1		
2	CH ₂	1		
3	CH ₂	1		
4	CH ₂	1		
5	CH ₂	1		
6	CH ₂	1		
7	CH ₂	1		
8	CH ₂	0		

9	CH ₂	0		
10	CH ₂	0		
11	CH ₂	0		
12	CH ₂	0		
13	CH ₂	0		
14	CH ₂	0		
15	CH ₂	0		
16	CH ₂	0		
17	CH ₂	0		
18	CH ₂	0		
19	CH ₂	0		
20	CH ₂	0		
21	bond	0		

22	bond	0		
23	bond	0		

and pharmaceutically acceptable salts thereof.

When a halogen atom is present in the compound of formula (I) it may be fluorine, 5 chlorine, bromine or iodine.

When the compound of formula (I) contains an alkyl group, whether alone or forming part of a larger group, e.g. alkoxy or alkylthio, the alkyl group may be straight chain, branched or cyclic, or combinations thereof, it is preferably methyl or ethyl.

When used herein the term aryl means a 5- to 6- membered aromatic ring for 10 example phenyl, or a 7 to 12 membered bicyclic ring system where at least one of the rings is aromatic for example naphthyl.

It will be appreciated that compounds of formula (I) may exist as *R* or *S* enantiomers. The present invention includes within its scope all such isomers, including 15 mixtures. Where additional chiral centres are present in compounds of formula (I), the present invention includes within its scope all possible diastereoisomers, including mixtures thereof. The different isomeric forms may be separated or resolved one from the other by conventional methods, or any given isomer may be obtained by conventional synthetic methods or by stereospecific or asymmetric syntheses.

It will be understood that the invention includes pharmaceutically acceptable 20 derivatives of compounds of formula (I) and that these are included within the scope of the invention.

Particular compounds according to the invention include those mentioned in the examples and their pharmaceutically acceptable derivatives.

As used herein "pharmaceutically acceptable derivative" includes any 25 pharmaceutically acceptable salt, ester or salt of such ester of a compound of formula (I) which, upon administration to the recipient is capable of providing (directly or indirectly) a compound of formula (I) or an active metabolite or residue thereof.

It will be appreciated that for use in medicine the salts of the compounds of formula (I) should be pharmaceutically acceptable. Suitable pharmaceutically acceptable salts will 30 be apparent to those skilled in the art and include acid addition salts formed with inorganic acids e.g. hydrochloric, hydrobromic, sulphuric, nitric or phosphoric acid; and organic acids e.g. succinic, maleic, acetic, fumaric, citric, tartaric, benzoic, p-toluenesulfonic, methanesulfonic or naphthalenesulfonic acid. Other salts e.g. oxalates, may be used, for 35 example in the isolation of compounds of formula (I) and are included within the scope of this invention. Also included within the scope of the invention are solvates and hydrates of compounds of formula (I).

Certain of the compounds of formula (I) may form acid addition salts with one or more equivalents of the acid. The present invention includes within its scope all possible stoichiometric and non-stoichiometric forms.

Since the compounds of formula (I) are intended for use in pharmaceutical compositions it will readily be understood that they are each preferably provided in substantially pure form, for example at least 60% pure, more suitably at least 75% pure and preferably at least 85%, especially at least 98% pure (% are on a weight for weight basis). Impure preparations of the compounds may be used for preparing the more pure forms used in the pharmaceutical compositions.

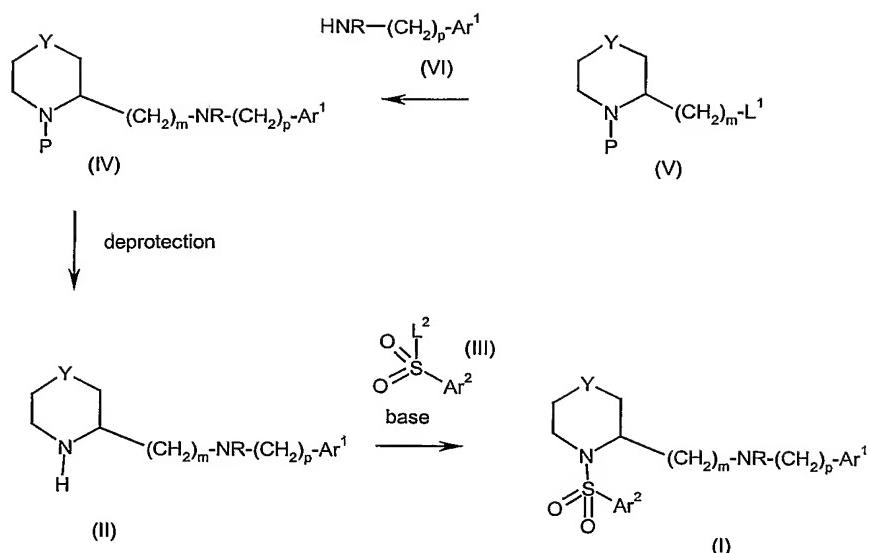
According to a further aspect of the present invention there is provided a process for the preparation of compounds of formula (I) and derivatives thereof. The following schemes detail some synthetic routes to compounds of the invention.

Schemes

- According to a further feature of the invention there is provided a process for the preparation of compounds of formula (I) and derivatives thereof. The following are examples of synthetic schemes that may be used to synthesise the compounds of the invention.
- Schemes 1a-c may be used for the synthesis of compounds where $q = 0$.
Scheme 2 may be used for the synthesis of compounds where $q = 0$ or 1.
Scheme 3-5 may be used for the synthesis of compounds where $q = 1$.
- The compounds labeled (I) in schemes 1 to 5 signify compounds that fall within the generic scope of formula (I).

Scheme 1a

30

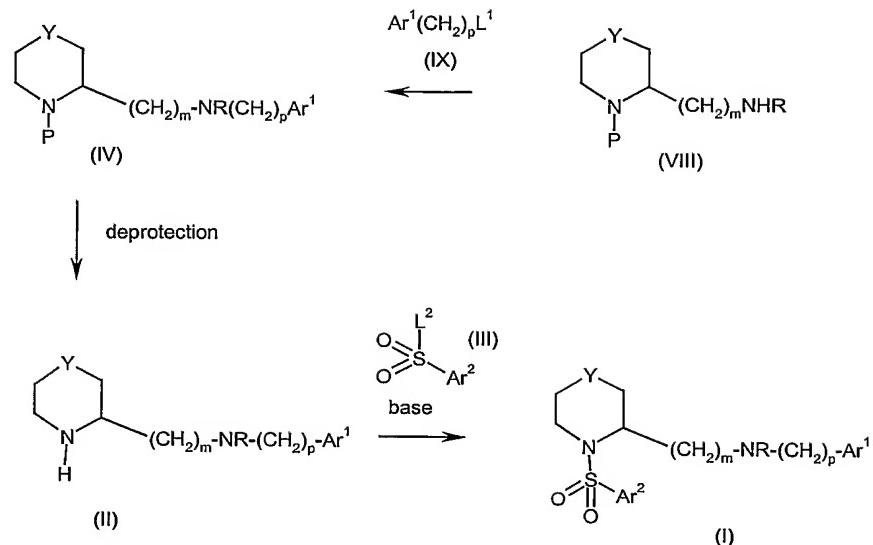


wherein Ar¹, Ar², Y, m, p and R are as defined for formula (I), q = 0, L¹ and L² are leaving groups, and P is a protecting group.

5 Examples of suitable leaving groups L¹ include halogen, hydroxy, OSO₂Me, OSO₂(4-tolyl). The reaction of (V) with (VI) preferably proceeds in an inert solvent such as N,N-dimethylformamide in the presence of a base such as triethylamine, sodium hydride or potassium t-butoxide.

An example of a suitable leaving group L^2 is halogen. Sulphonamide formation eg. (II) to (I) may be carried out in an inert solvent such as dichloromethane, in the presence of a base such as triethylamine.

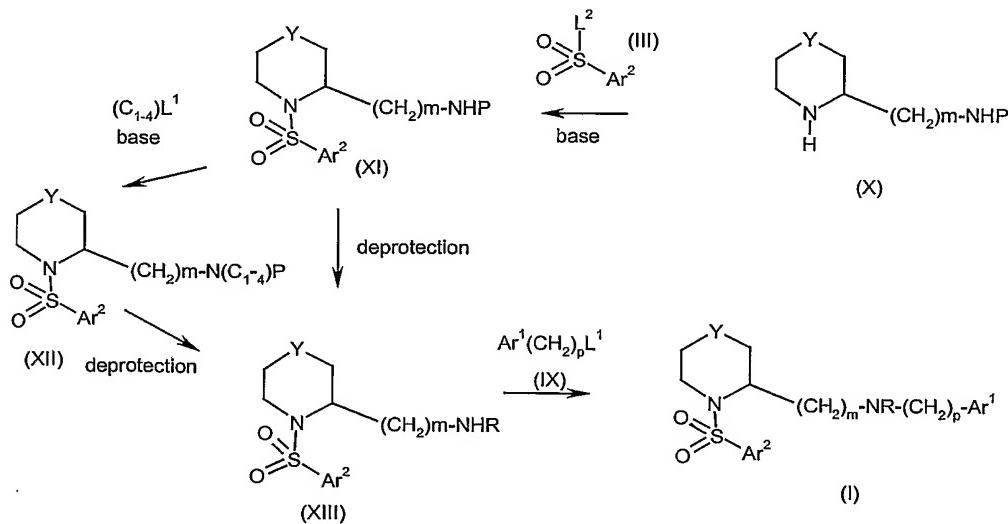
Examples of protecting groups P include *t*-butyloxycarbonyl, trifluoroacetyl, optionally substituted benzyl and benzyloxycarbonyl. Deprotection conditions are respectively, acid (e.g. trifluoroacetic acid in dichloromethane), base (e.g. sodium hydroxide in a solvent such as aqueous methanol) and catalytic hydrogenolysis in an inert solvent (e.g. using palladium on charcoal in a lower alcohol or ethyl acetate).

Scheme 1b

5 Reaction of (VIII) with (IX) proceeds in an inert solvent such as dimethylformamide or xylene in the presence of a base such as potassium carbonate or diisopropylethylamine, preferably at elevated temperatures. P can be a protecting group or H.

Alternatively where m is 1 and p is 0 or 1 compounds maybe prepared as shown in scheme 1c.

10

Scheme 1c

Reaction of (XI) with an alkylating agent $(\text{C}_{1-4})\text{L}^1$ proceeds in the presence of a base such as sodium hydride in an inert solvent such as dimethylformamide.

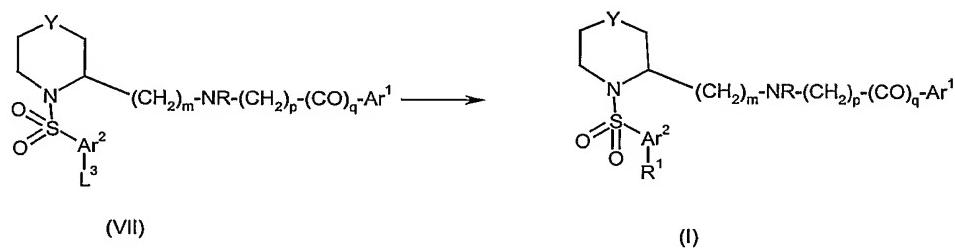
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Compounds of formula (V), (VI), (IX), (X) are known in the literature or can be prepared by known methods. Compounds (VIII) can be prepared by known methods.

Within the schemes above there is scope for functional group interconversion; for example in compound (V), conversion of one value of L¹ to another value of L¹; or in compounds (IV) conversion of protecting group P for another protecting group P, or conversion of one compound of formula (I) to another of formula (I) by interconversion of substituents. Where Y = NQ, Q may also represent a protecting group P in the above schemes.

When R¹ is an aromatic group, the substituent R¹ may be introduced at the final stage as illustrated in Scheme 2 by reaction of a compound of formula (VII) where L³ represents a leaving group such as halogen (preferably bromo or iodo) or trifluoromethylsulfonyloxy, and all other variables are as previously defined, with a reagent R¹M, where M is the residue of an organometallic species e.g. B(OH)₂ or trialkylstanny. Such a process may be carried out in an inert solvent such as 1,2-dimethoxyethane or 1,4-dioxan, in the presence of a transition metal catalyst such as Pd(PPh₃)₄.

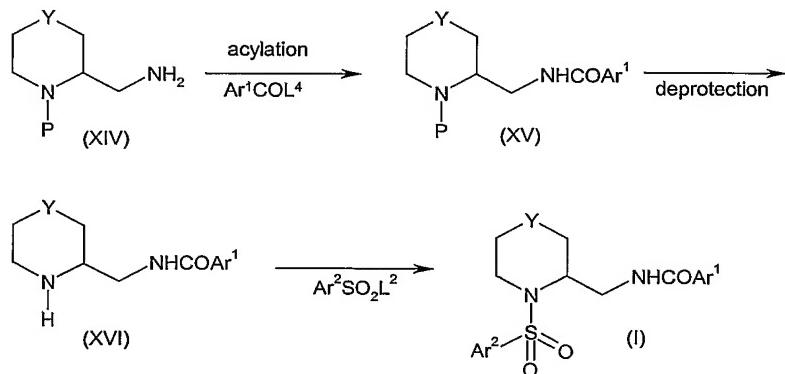
15 Scheme 2



Wherein Ar², m, p, q, Ar¹, R, R¹ and Y are as defined for compounds of formula (I). L³ is a leaving group.

20

Scheme 3

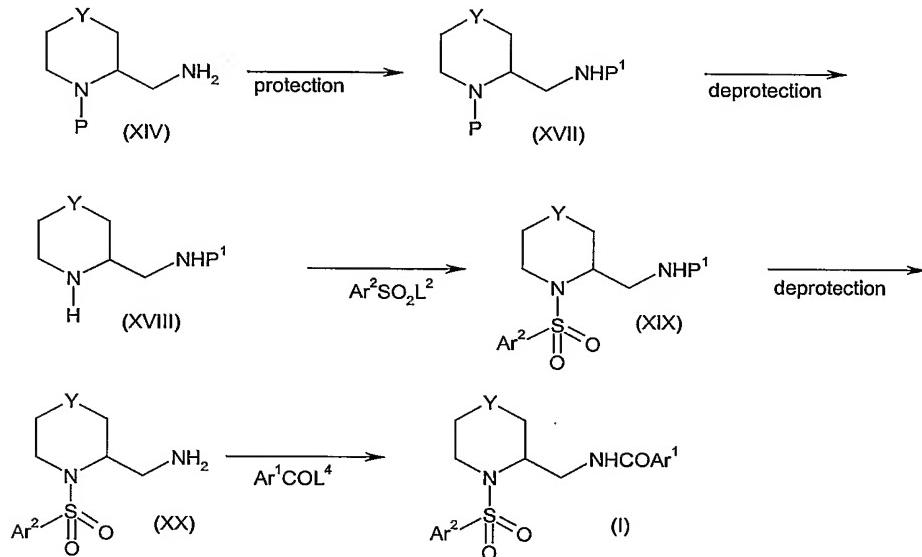


wherein Y, Ar¹ and Ar² are as defined for formula (I), P is a protecting group, L² is a leaving group as defined above and L⁴ is a leaving group.

Examples of suitable leaving groups L⁴ include halogen, hydroxy, OC(=O)alkyl OC(=O)O-alkyl and OSO₂Me. Acylation may be carried out using a wide range of known acylation conditions, e.g. in an inert solvent such as dichloromethane, in the presence of a base such as triethylamine. Alternatively these steps may be carried out when L⁴ represents hydroxy, in which case the reaction

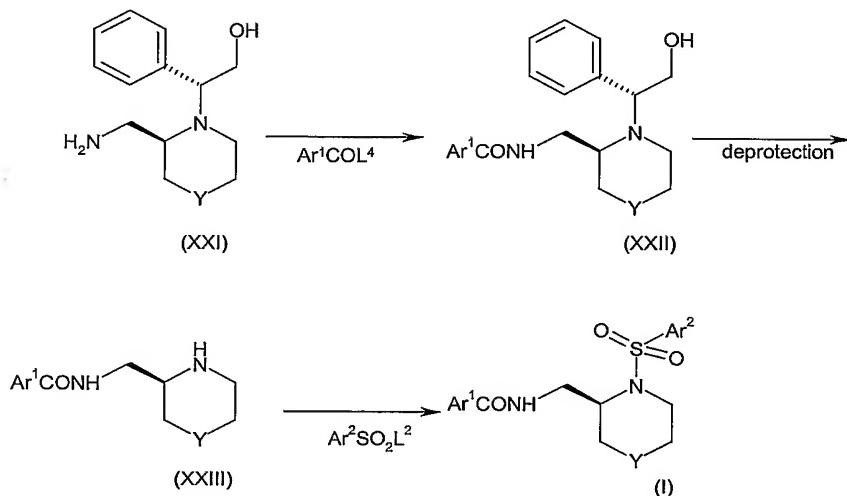
takes place in an inert solvent such as dichloromethane in the presence of a diimide reagent such as 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride, and an activator such as 1-hydroxybenzotriazole.

5 Scheme 4



wherein Y, Ar¹ and Ar² are as defined for formula (I), P and P¹ are protecting groups and L² and L⁴ are leaving groups as defined above. Examples of protecting groups P and P¹ are given in scheme 1a.

Scheme 5



15 wherein Y, Ar¹ and Ar² are as defined for formula (I), and L¹ and L⁴ are leaving groups as described above.

Compound (XXI) may be prepared as described in O. Froelich et al., *Tet. Asym.* 1993, 4 (11), 2335 and references therein.

5 The starting materials for use in Schemes 1 to 5 are commercially available, known in the literature or can be prepared by known methods. Within the schemes above there is scope for functional group interconversion, and for conversion of one value of L¹ to L⁴ to another value of L¹ to L⁴; or conversion of protecting group P or P¹ to another protecting group P or P¹, or conversion of one compound of formula (I) to another of formula (I) by interconversion of substituents. Where Y = NQ, Q may also represent a protecting group P in the above schemes.

10 The compounds of formula (I) may be prepared singly or as compound libraries comprising at least 2, e.g. 5 to 1000, preferably 10 to 100 compounds of formula (I). Compound libraries may be prepared by a combinatorial 'split and mix' approach or by 15 multiple parallel synthesis using either solution phase or solid phase chemistry, by procedures known to those skilled in the art.

15 Thus according to a further aspect of the invention there is provided a compound library comprising at least 2 compounds of formula (I), or pharmaceutically acceptable derivatives thereof.

Pharmaceutically acceptable salts may be prepared conventionally by reaction with the appropriate acid or acid derivative.

20 The compounds of formula (I) and their pharmaceutically acceptable derivatives are useful for the treatment of diseases or disorders where an antagonist of a human Orexin receptor is required such as obesity and diabetes; prolactinoma; hypoprolactinemia; 25 hypothalamic disorders of growth hormone deficiency; idiopathic growth hormone deficiency; Cushings syndrome/disease; hypothalamic-adrenal dysfunction; dwarfism; sleep disorders; sleep apnea; narcolepsy; insomnia; parasomnia; jet-lag syndrome; sleep disturbances associated with diseases such as neurological disorders, neuropathic pain and 30 restless leg syndrome; heart and lung diseases; depression; anxiety; addictions; obsessive compulsive disorder; affective neurosis/disorder; depressive neurosis/disorder; anxiety neurosis; dysthymic disorder; behaviour disorder; mood disorder; sexual dysfunction; psychosexual dysfunction; sex disorder; sexual disorder; schizophrenia; manic depression; delerium; dementia; bulimia and hypopituitarism. Additionally the compounds of formula 35 (I) and pharmaceutically acceptable derivatives are useful for the treatment of stroke, particularly ischemic or haemorrhagic and/or in blocking an emetic response i.e. nausea and vomiting.

35 The compounds of formula (I) and their pharmaceutically acceptable derivatives are particularly useful for the treatment of obesity, including obesity associated with Type 2 diabetes, and sleep disorders. Additionally the compounds of formula (I) and pharmaceutically acceptable derivatives are useful for the treatment of stroke, particularly 40 ischemic or haemorrhagic and/or in blocking an emetic response i.e. nausea and vomiting.

Other diseases or disorders which may be treated in accordance with the invention include disturbed biological and circadian rhythms; adrenohypophysis disease; hypophysis disease; hypophysis tumor / adenoma; adrenohypophysis hypofunction; functional or psychogenic amenorrhea; adrenohypophysis hyperfunction; migraine; hyperalgesia; pain; enhanced or exaggerated sensitivity to pain such as hyperalgesia, causalgia and allodynia; acute pain; burn pain; atypical facial pain; neuropathic pain; back pain; complex regional

pain syndromes I and II; arthritic pain; sports injury pain; pain related to infection e.g. HIV, post-polio syndrome and post-herpetic neuralgia; phantom limb pain; labour pain; cancer pain; post-chemotherapy pain; post-stroke pain; post-operative pain; neuralgia; and tolerance to narcotics or withdrawal from narcotics.

5 The invention also provides a method of treating or preventing diseases or disorders where an antagonist of a human Orexin receptor is required, which comprises administering to a subject in need thereof an effective amount of a compound of formula (I), or a pharmaceutically acceptable derivative thereof.

10 The invention also provides a compound of formula (I), or a pharmaceutically acceptable derivative thereof, for use in the treatment or prophylaxis of diseases or disorders where an antagonist of a human Orexin receptor is required.

15 The invention also provides the use of a compound of formula (I), or a pharmaceutically acceptable derivative thereof, in the manufacture of a medicament for the treatment or prophylaxis of diseases or disorders where an antagonist of a human Orexin receptor is required.

For use in therapy the compounds of the invention are usually administered as a pharmaceutical composition. The invention also provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable derivative thereof, and a pharmaceutically acceptable carrier.

20 The compounds of formula (I) and their pharmaceutically acceptable derivatives may be administered by any convenient method, e.g. by oral, parenteral, buccal, sublingual, nasal, rectal or transdermal administration, and the pharmaceutical compositions adapted accordingly.

25 The compounds of formula (I) and their pharmaceutically acceptable derivatives which are active when given orally can be formulated as liquids or solids, e.g. as syrups, suspensions, emulsions, tablets, capsules or lozenges.

30 A liquid formulation will generally consist of a suspension or solution of the active ingredient in a suitable liquid carrier(s) e.g. an aqueous solvent such as water, ethanol or glycerine, or a non-aqueous solvent, such as polyethylene glycol or an oil. The formulation may also contain a suspending agent, preservative, flavouring and/or colouring agent.

A composition in the form of a tablet can be prepared using any suitable pharmaceutical carrier(s) routinely used for preparing solid formulations, such as magnesium stearate, starch, lactose, sucrose and cellulose.

35 A composition in the form of a capsule can be prepared using routine encapsulation procedures, e.g. pellets containing the active ingredient can be prepared using standard carriers and then filled into a hard gelatin capsule; alternatively a dispersion or suspension can be prepared using any suitable pharmaceutical carrier(s), e.g. aqueous gums, celluloses, silicates or oils and the dispersion or suspension then filled into a soft gelatin capsule.

40 Typical parenteral compositions consist of a solution or suspension of the active ingredient in a sterile aqueous carrier or parenterally acceptable oil, e.g. polyethylene glycol, polyvinyl pyrrolidone, lecithin, arachis oil or sesame oil. Alternatively, the solution can be lyophilised and then reconstituted with a suitable solvent just prior to administration.

Compositions for nasal administration may conveniently be formulated as aerosols, drops, gels and powders. Aerosol formulations typically comprise a solution or fine suspension of the active ingredient in a pharmaceutically acceptable aqueous or non-aqueous solvent and are usually presented in single or multidose quantities in sterile form in a sealed container which can take the form of a cartridge or refill for use with an atomising device. Alternatively the sealed container may be a disposable dispensing device such as a single dose nasal inhaler or an aerosol dispenser fitted with a metering valve. Where the dosage form comprises an aerosol dispenser, it will contain a propellant which can be a compressed gas e.g. air, or an organic propellant such as a fluorochlorohydrocarbon or hydrofluorocarbon. Aerosol dosage forms can also take the form of pump-atomisers.

10 Compositions suitable for buccal or sublingual administration include tablets, lozenges and pastilles where the active ingredient is formulated with a carrier such as sugar and acacia, tragacanth, or gelatin and glycerin.

15 Compositions for rectal administration are conveniently in the form of suppositories containing a conventional suppository base such as cocoa butter.

Compositions suitable for transdermal administration include ointments, gels and patches.

Preferably the composition is in unit dose form such as a tablet, capsule or ampoule.

20 The dose of the compound of formula (I), or a pharmaceutically acceptable derivative thereof, used in the treatment or prophylaxis of the abovementioned disorders or diseases will vary in the usual way with the particular disorder or disease being treated, the weight of the subject and other similar factors. However, as a general rule, suitable unit doses may be 0.05 to 1000 mg, more suitably 0.05 to 500 mg. Unit doses may be administered more than once a day for example two or three times a day, so that the total daily dosage is in the range of about 0.01 to 100 mg/kg; and such therapy may extend for a number of weeks or months. In the case of pharmaceutically acceptable derivatives the above figures are calculated as the parent compound of formula (I).

25 No toxicological effects are indicated/expected when a compound of formula (I) is administered in the above mentioned dosage range.

30 Human Orexin-A has the amino acid sequence:

pyroGlu Pro Leu Pro Asp Cys Cys Arg Gln Lys Thr Cys Ser Cys Arg Leu

1 5 10 15

Tyr Glu Leu Leu His Gly Ala Gly Asn His Ala Ala Gly Ile Leu Thr

20 25 30

35 Leu-NH₂

Orexin-A can be employed in screening procedures for compounds which inhibit the ligand's activation of the orexin-1 receptor.

40 In general, such screening procedures involve providing appropriate cells which express the orexin-1 receptor on their surface. Such cells include cells from mammals, yeast, Drosophila or *E. coli*. In particular, a polynucleotide encoding the orexin-1 receptor is used to transfet cells to express the receptor. The expressed receptor is then contacted with a test compound and an orexin-1 receptor ligand to observe inhibition of a functional

response. One such screening procedure involves the use of melanophores which are transfected to express the orexin-1 receptor, as described in WO 92/01810.

Another screening procedure involves introducing RNA encoding the orexin-1 receptor into *Xenopus* oocytes to transiently express the receptor. The receptor oocytes are then contacted with a receptor ligand and a test compound, followed by detection of inhibition of a signal in the case of screening for compounds which are thought to inhibit activation of the receptor by the ligand.

Another method involves screening for compounds which inhibit activation of the receptor by determining inhibition of binding of a labelled orexin-1 receptor ligand to cells which have the receptor on their surface. This method involves transfecting a eukaryotic cell with DNA encoding the orexin-1 receptor such that the cell expresses the receptor on its surface and contacting the cell or cell membrane preparation with a compound in the presence of a labelled form of an orexin-1 receptor ligand. The ligand may contain a radioactive label. The amount of labelled ligand bound to the receptors is measured, e.g. by measuring radioactivity.

Yet another screening technique involves the use of FLIPR equipment for high throughput screening of test compounds that inhibit mobilisation of intracellular calcium ions, or other ions, by affecting the interaction of an orexin-1 receptor ligand with the orexin-1 receptor.

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

The following Examples illustrate the preparation of pharmacologically active compounds of the invention. The Descriptions D1-D14 illustrate the preparation of intermediates to compounds of the invention.

Description 1: 2,2,2-Trifluoro-N-[(S)-1-((R)-2-hydroxy-1-phenyl-ethyl)-piperidin-2-ylmethyl]-acetamide

(R)-2-[(S)-2-Aminomethyl-piperidin-1-yl]-2-phenyl-ethanol (20.0g) (Froelich, Olivier; Desos, Patrice; Bonin, Martine; Quirion, Jean-Charles; Husson, Henri-Philippe; Zhu, Jieping., J. Org. Chem. 1996, 61, 6700) and triethylamine (13.0ml) were dissolved in dichloromethane (500ml), cooled to 0°C and trifluoroacetic anhydride (12.66ml) added dropwise. The mixture was warmed to room temperature and stirred overnight. The organic phase was washed with water, separated, dried and solvent removed at reduced pressure. The residue was column chromatographed [silica gel, 0 – 10% (9:1 methanol/ammonia) in dichloromethane eluant] to give the title compound (28.0g) as a yellow oil. Mass spectrum (API): Found 331 (MH^+). $C_{16}H_{21}F_3N_2O_2$ requires 330. $[\alpha]_D - 55^\circ @ 28^\circ c = 1\%$ in chloroform

Description 2: 2,2,2-Trifluoro-N-(S)-1-piperidin-2-ylmethyl-acetamide

The product from D1 (28.0g) was dissolved in ethanol (200ml) containing Pearlmans catalyst (2.0g) and shaken under a hydrogen atmosphere (50psi) at 50°C for 3 hours. The

reaction mixture was filtered and solvent removed at reduced pressure. The residue was column chromatographed (silica gel, 0 – 10% (9:1 methanol/ammonia) in dichloromethane eluant) to give the title compound (14.18g) as a colourless oil. Mass spectrum (API⁺): Found 211 (MH⁺). C₈H₁₃F₃N₂O requires 210. [α]_D +18°@ 28° c = 1% in chloroform. ¹H NMR δ: (d⁶-DMSO) 1.07 (1H, m), 1.32 (2H, m), 1.35 – 1.60 (2H, m), 1.72 (1H, m), 2.54 (1H, t), 2.70 (1H, m), 3.00 (1H, d), 3.17 (3H, m), 9.30 (1H, br. s.).

Description 3: (S)-2-[(2,2,2-Trifluoro-ethanoylamino)-methyl]-piperidine-1-carboxylic acid *tert* butyl ester

The product from D2 (14.18g) was dissolved in dichloromethane (250ml) and treated with di-*tert*-butyl dicarbonate (14.95g). The mixture was stirred for 16h, washed with water, 2N hydrochloric acid and saturated brine, dried and solvent removed at reduced pressure to give the title compound (18.3g). Mass spectrum (API⁺): Found 311 (MH⁺). C₁₃H₂₁F₃N₂O₃ requires 310. [α]_D -94°@ 28° c = 1% in chloroform. ¹H NMR δ: (d⁶-DMSO) 1.27 (1H, m), 1.36, 1.47 (9H, s), 1.49 – 1.58 (5H, m), 2.88 (1H, m), 3.22 (1H, m), 3.49 (1H, m), 3.84 (1H, m), 4.34 (1H, m) and 9.42 (1H, br. s.).

Description 4: (S) 2-Aminomethyl-piperidine-1-carboxylic acid *tert* butyl ester

The product from D3 (18.2g) was dissolved in methanol (500ml) and treated with potassium carbonate (16.1g). After stirring for 16h solvent was removed at reduced pressure and the residue partitioned between dichloromethane/water. The organic phase was separated, washed with brine, dried and solvent removed at reduced pressure. the residue was column chromatographed (silica gel, 0 – 10% (9:1 methanol/ammonia) in dichloromethane eluant) to give the title compound (8.82g). Mass spectrum (API⁺): Found 215 (MH⁺). C₁₁H₂₂N₂O₂ requires 214. [α]_D -32.2°@ 28° c = 1% in chloroform. ¹H NMR δ: 1.20 – 1.70 (8H, m), 1.46 (9H, s), 2.64 – 2.80 (2H, m), 2.94 (1H, dd), 3.99 (1H, m) and 4.15 (1H, m).

Description 5: (S)-2-(((1-Benzofuran-4-yl-methanoyl)-amino)-methyl)-piperidine-1-carboxylic acid *tert*-butyl ester

To the amine from D4 (2.14g) in dichloromethane (50ml) was added benzofuran-4-carboxylic acid (1.62g), followed by 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.92g) and 1-hydroxybenzotriazole hydrate (0.1g) and the mixture stirred at room temperature for 18h. The reaction mixture was diluted with dichloromethane and washed with saturated sodium bicarbonate solution. The organic phase was dried, evaporated and the residue chromatographed on silica gel eluting with a pentane/ethyl acetate gradient to afford the title product as a colourless solid (3g). Mass spectrum (API⁺): Found 381 (MNa⁺). C₂₀H₂₆N₂O₄ requires 358.

Description 6: Benzofuran-4-carboxylic acid ((S)-1-piperidin-2-ylmethyl)-amide

To the product from D5 (2.9g) in dichloromethane (100ml) was added trifluoroacetic acid (15ml) at room temperature. After 3.5h the mixture was evaporated and the residue partitioned between dichloromethane and 1M sodium hydroxide. The aqueous phase was

re-extracted with dichloromethane and the combined organic phases dried and evaporated *in vacuo* to afford the title product as a colourless solid (2.17g). Mass spectrum (API⁺): Found 259 (MH⁺). C₁₅H₁₈N₂O₂ requires 258.

5 **Description 7: (S)-2-[(6,7-Difluoroquinoxalin-2-ylamino)methyl]-piperidine-1-carboxylic acid *tert* butyl ester**

The amine D4 (0.607g), and 2-chloro-6,7-difluoroquinoxaline *McQuaid et. al. J. Med. Chem.* (1992), 35(18), 3319-24 (0.569g) were dissolved in dimethylformamide (1ml) and heated to 90 °C for 5 days under an atmosphere of argon. After cooling, the reaction solution was partitioned between ethyl acetate and water. The organic layer was washed with water, saturated brine, dried and evaporated. The residue was chromatographed over silica gel, eluting with a gradient of 10 to 50% ethyl acetate in hexane. The title compound was obtained as a pale yellow solid (0.460g), MH⁺ 379. C₁₉H₂₄F₂N₄O₂ requires 378.

10

15 **Description 8: (S)-2-[(6,7-Difluoroquinoxalin-2-ylamino)methyl]-piperidine**

The product from D7 (0.460g) was dissolved in trifluoroacetic acid (10ml) and stirred at room temperature for 3 hours. The solution was then evaporated and the residue chromatographed over silica gel, eluting with 0 to 10% (9:1 methanol – concentrated ammonia solution) in dichloromethane. The title compound was obtained as a pale yellow foam (0.286g), MH⁺ 279. C₁₄H₁₆F₂N₄ requires 278.

20

Description 9: (S)-2-[(5-Cyano-pyridin-2-ylamino)-methyl]-piperidine-1-carboxylic acid *tert* butyl ester.

The title compound (1.54g) was prepared from D4 (2.0g) and 2-chloro-5-cyanopyridine (1.29g) in the presence of diisopropylethylamine (1.21g) according to the method of D7. Mass spectrum (API⁺): Found 317 (MH⁺). C₁₇H₂₄N₄O₂ requires 316.

25 **Description 10: (S)-6-[(Piperidin-2-ylmethyl)-amino]-nicotinonitrile**

The title compound (1.56g) was prepared from the compound of D9 (1.53g) and trifluoroacetic acid according to the method of D8. Mass spectrum (API⁺): Found 217 (MH⁺). C₁₂H₁₆N₄ requires 216.

30

Description 11: (S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-carboxylic acid *tert* butyl ester

35 (S)-2-Aminomethyl-pyrrolidine-1-carboxylic acid *tert* butyl ester (5g, 0.025mol) and 5-bromo-2-chloropyrimidine (4.83g, 0.025mol) were combined in xylene (150ml) containing potassium carbonate (10.35g, 0.075mol) and diisopropylethylamine (12.9ml, 0.075mol) and heated under argon at 100°C for 20h. The mixture was cooled to room temperature, filtered and solvent removed at reduced pressure. The residue was column chromatographed (silica gel, pentane – 30% ethyl acetate/pentane). The appropriate fractions were collected, solvent removed at reduced pressure to give the title compound (4.7g, 53%) as a colourless gum

40 Mass spectrum (API⁺): Found 257 (MH⁺ - *tert* BOC). C₁₄H₂₁⁷⁹BrN₄O₂ requires 356.

Description 12: (S)-(5-Bromo-pyrimidin-2-yl)-pyrrolidin-2-ylmethyl-amine

To a solution of D11 (4.7g, 13mmol) in dichloromethane (100ml) was added trifluoroacetic acid (15ml) at room temperature. After 18h the reaction mixture was evaporated and partitioned between dichloromethane and 1M sodium hydroxide. The aqueous phase was extracted with dichloromethane and the combined extracts dried and evaporated to afford the title product (2.72g, 80%). Mass spectrum (API⁺): Found 257 (MH⁺). C₉H₁₃N₄⁷⁹Br requires 256.

Description 13: (S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-piperidine-1-carboxylic acid tert butyl carbonate.

The amine from D4 (1g), 5-bromo-2-chloropyrimidine (0.9g) were combined in xylene (20ml) containing potassium carbonate (1.29g) and diisopropylethylamine (2.43g) and warmed to reflux for 48h. The mixture was cooled to room temperature, filtered and solvent removed at reduced pressure. The residue was column chromatographed (silica gel, pentane – 25% ethyl acetate/pentane). The appropriate fractions were collected, solvent removed at reduced pressure to give the title compound (1.43g) as a colourless gum. Mass spectrum (API⁺): Found 271 (MH⁺ - tert BOC). C₁₅H₂₃⁷⁹BrN₄O₂ requires 370.

Description 14: (S)-(5-Bromo-pyrimidin-2-yl)-piperidin-2-ylmethyl-amine dihydrochloride

The compound of D13 (2.1 g) was stirred in a mixture of 4M HCl in dioxan/methanol (1:1) for 4 h. Solvent was removed at reduced pressure to give the title compound (1.4g) as a foam. Mass spectrum (API⁺): Found 271 (MH⁺). C₁₀H₁₅⁷⁹BrN₄ requires 270.

Example 1: Benzofuran-4-carboxylic acid ((S)-1-(naphthalene-1-sulfonyl)-piperidin-2-ylmethyl)amide

1-Naphthalene sulfonyl chloride (0.105g) was added to the amine D6 (0.1g) and triethylamine (0.16ml) in dichloromethane (4ml) at room temperature. After 18h the reaction mixture was washed with saturated sodium bicarbonate solution and the organic layer added directly onto a dry prepacked silica gel cartridge which was eluted with an ethyl acetate/pentane gradient to afford the title product (0.146g). Mass spectrum (Electrospray LC/MS): Found 449 (MH⁺). C₂₅H₂₄N₂O₄S requires 448.

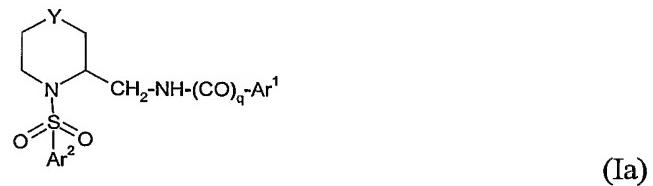
Example 2: Benzofuran-4-carboxylic acid ((S)-1-(biphenyl-2-sulfonyl)-piperidin-2-ylmethyl)-amide

A mixture of the product from Example 7 (0.465g), phenylboronic acid (0.108g) and sodium carbonate (0.470g) in dimethoxyethane (12ml) and water (12ml) was deoxygenated, tetrakis(triphenylphosphine)palladium (0) ((0.185g) added and the reaction heated under argon at 100°C for 3h. The cooled mixture was filtered, diluted with water and extracted with ethyl acetate. The extracts were dried and evaporated *in vacuo* to a brown gum that was purified on silica gel eluting with an ethyl acetate/pentane gradient to afford the title

product (0.100g). Mass spectrum (Electrospray LC/MS): Found 475 (MH^+). $C_{27}H_{26}N_2O_4S$ requires 474.

In a similar manner Examples 3-23 in the table below were prepared from the amines
5 described in the descriptions above and the appropriate sulphonyl chloride.

The compounds of examples 3 to 23 have the core structure (Ia)



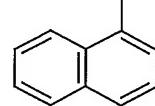
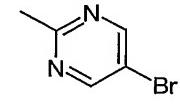
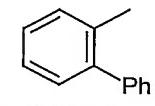
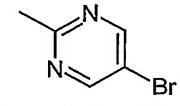
10

wherein Y, q, Ar¹ and Ar² are as indicated in table 2:

Table 2

Example	Y	q	Ar ²	Ar ¹	Mass Spectrum (Electrospray LC/MS), API^+
3	CH ₂	1			Found: 449 (MH^+) $C_{25}H_{24}N_2O_4S$ requires 448.
4	CH ₂	1			Found: 483 (MH^+) $C_{22}H_{21}F_3N_2O_5S$ requires 482.
5	CH ₂	1			Found: 429 (MH^+) $C_{22}H_{24}N_2O_5S$ requires 428.
6	CH ₂	1			Found: 429 (MH^+) $C_{22}H_{24}N_2O_5S$ requires 428.
7	CH ₂	1			Found: 525 (MH^+) $C_{21}H_{21}IN_2O_4S$ requires 524.
8	CH ₂	0			Found: 469 (MH^+) $C_{24}H_{22}F_2N_4O_2S$ requires 468.

9	CH ₂	0			Found: 469 (MH ⁺) C ₂₄ H ₂₂ F ₂ N ₄ O ₂ S requires 468.
10	CH ₂	0			Found: 449 (MH ⁺) C ₂₁ H ₂₂ F ₂ N ₄ O ₃ S requires 448.
11	CH ₂	0			Found: 449 (MH ⁺) C ₂₁ H ₂₂ F ₂ N ₄ O ₃ S requires 448.
12	CH ₂	0			Found: 461 (MH ⁺) C ₂₃ H ₂₆ F ₂ N ₄ O ₂ S requires 460.
13	CH ₂	0			Found: 433 (MH ⁺) C ₂₁ H ₂₂ F ₂ N ₄ O ₂ S requires 432.
14	CH ₂	0			Found: 453 (MH ⁺) C ₂₀ H ₁₉ ³⁵ ClF ₂ N ₄ O ₂ S requires 452.
15	CH ₂	0			Found: 453 (MH ⁺) C ₂₀ H ₁₉ ³⁵ ClF ₂ N ₄ O ₂ S requires 452.
16	CH ₂	0			Found: 433 (MH ⁺) C ₂₁ H ₂₂ F ₂ N ₄ O ₂ S requires 432.
17	CH ₂	0			Found: 487 (MH ⁺) C ₂₁ H ₁₉ F ₅ N ₄ O ₂ S requires 486.
18	CH ₂	0			Found: 407 (MH ⁺) C ₂₂ H ₂₂ N ₄ O ₂ S requires 406.
19	CH ₂	0			Found: 461 (MH ⁺) C ₂₀ H ₂₁ ⁷⁹ BrN ₄ O ₂ S requires 460.
20	CH ₂	0			Found: 461 (MH ⁺) C ₂₀ H ₂₁ ⁷⁹ BrN ₄ O ₂ S requires 460.
21	bond	0			Found: 481 (MH ⁺) C ₁₆ H ₁₆ ⁷⁹ BrF ₃ N ₄ O ₃ S requires 480.

22	bond	0			Found: 447 (MH^+) $C_{19}H_{19}{^{79}Br}N_4O_2S$ requires 446.
23	bond	0			Found: 473 (MH^+) $C_{21}H_{21}{^{79}Br}N_4O_2S$ requires 472.

It is understood that the present invention covers all combinations of particular and preferred groups described herein above.

5

Determination of Orexin-1 Receptor Antagonist Activity

The orexin-1 receptor antagonist activity of the compounds of formula (I) was determined in accordance with the following experimental method.

10

Experimental Method

CHO-DG44 cells expressing the human orexin-1 receptor were grown in cell medium (MEM medium with Earl's salts) containing 2 mM L-Glutamine, 0.4 mg/mL G418 Sulphate from GIBCO BRL and 10% heat inactivated fetal calf serum from Gibco BRL.

15

The cells were seeded at 20,000 cells/100 μ L/well into 96-well black clear bottom sterile plates from Costar which had been pre-coated with 10 μ g/well of poly-L-lysine from SIGMA. The seeded plates were incubated overnight at 37C in 5% CO₂.

20

Agonists were prepared as 1 mM stocks in water:DMSO (1:1). EC50 values (the concentration required to produce 50% maximal response) were estimated using 11x half log unit dilutions (Biomek 2000, Beckman) in Tyrode's buffer containing probenecid (10 mM HEPES with 145mM NaCl, 10mM glucose, 2.5 mM KCl, 1.5 mM CaCl₂, 1.2 mM MgCl₂ and 2.5mM probenecid; pH7.4). Antagonists were prepared as 10 mM stocks in DMSO (100%). Antagonist IC50 values (the concentration of compound needed to inhibit 50% of the agonist response) were determined against 3.0 nM human orexin-A using 11x half log unit dilutions in Tyrode's buffer containing 10% DMSO and probenecid.

25

On the day of assay 50 μ L of cell medium containing probenecid (Sigma) and Fluo3AM (Texas Fluorescence Laboratories) was added (Quadra, Tomtec) to each well to give final concentrations of 2.5 mM and 4 μ M, respectively. The 96-well plates were incubated for 60 min at 37C in 5% CO₂. The loading solution containing dye was then aspirated and cells were washed with 4x150 μ L Tyrode's buffer containing probenecid and 0.1% gelatin (Denley Cell Wash). The volume of buffer left in each well was 125 μ L. Antagonist or buffer (25 μ L) was added (Quadra) the cell plates gently shaken and incubated at 37C in 5% CO₂ for 30 minutes. Cell plates were then transferred to the Fluorescent Imaging Plate Reader (FLIPR, Molecular Devices) instrument. Prior to drug addition a single image of the cell plate was taken (signal test), to evaluate dye loading consistency. The run protocol used 60 images taken at 1 second intervals followed by a further 24 images at 5 second intervals. Agonists were added (by the FLIPR) after 20 seconds (during

continuous reading). From each well, peak fluorescence was determined over the whole assay period and the mean of readings 1-19 inclusive was subtracted from this figure. The peak increase in fluorescence was plotted against compound concentration and iteratively curve fitted using a four parameter logistic fit (as described by Bowen and Jerman, *TiPS*, 1995, **16**, 413-417) to generate a concentration effect value. Antagonist Kb values were calculated using the equation:

$$Kb = IC50 / (1 + ([3] / EC50])$$

where EC50 was the potency of human orexin-A determined in the assay (in nM terms) and IC50 is expressed in molar terms.

Compounds of Examples tested according to this method had pKb values in the range 6.9 to 8.6 at the human cloned orexin-1 receptor.

Determination of Orexin-2 Receptor Antagonist Activity

The orexin-2 receptor antagonist activity of the compounds of formula (I) was determined in accordance with the following experimental method.

Experimental Method

CHO-DG44 cells expressing the human orexin-2 receptor were grown in cell medium (MEM medium with Earl's salts) containing 2 mM L-Glutamine, 0.4 mg/mL G418 Sulphate from GIBCO BRL and 10% heat inactivated fetal calf serum from Gibco BRL. The cells were seeded at 20,000 cells/100 µl/well into 96-well black clear bottom sterile plates from Costar which had been pre-coated with 10 µg/well of poly-L-lysine from SIGMA. The seeded plates were incubated overnight at 37C in 5% CO₂.

Agonists were prepared as 1 mM stocks in water:DMSO (1:1). EC50 values (the concentration required to produce 50% maximal response) were estimated using 11x half log unit dilutions (Biomek 2000, Beckman) in Tyrode's buffer containing probenecid (10 mM HEPES with 145mM NaCl, 10mM glucose, 2.5 mM KCl, 1.5 mM CaCl₂, 1.2 mM MgCl₂ and 2.5mM probenecid; pH7.4). Antagonists were prepared as 10 mM stocks in DMSO (100%). Antagonist IC50 values (the concentration of compound needed to inhibit 50% of the agonist response) were determined against 10.0 nM human orexin-A using 11x half log unit dilutions in Tyrode's buffer containing 10% DMSO and probenecid.

On the day of assay 50 µl of cell medium containing probenecid (Sigma) and Fluo3AM (Texas Fluorescence Laboratories) was added (Quadra, Tomtec) to each well to give final concentrations of 2.5 mM and 4 µM, respectively. The 96-well plates were incubated for 60 min at 37C in 5% CO₂. The loading solution containing dye was then aspirated and cells were washed with 4x150 µl Tyrode's buffer containing probenecid and 0.1% gelatin (Denley Cell Wash). The volume of buffer left in each well was 125 µl. Antagonist or buffer (25 µl) was added (Quadra) the cell plates gently shaken and incubated at 37C in 5% CO₂ for 30 min. Cell plates were then transferred to the Fluorescent Imaging Plate Reader (FLIPR, Molecular Devices) instrument. Prior to drug addition a single image of the cell plate was taken (signal test), to evaluate dye loading consistency. The run protocol used 60 images taken at 1 second intervals followed by a further 24 images at 5

second intervals. Agonists were added (by the FLIPR) after 20 sec (during continuous reading). From each well, peak fluorescence was determined over the whole assay period and the mean of readings 1-19 inclusive was subtracted from this figure. The peak increase in fluorescence was plotted against compound concentration and iteratively curve fitted
5 using a four parameter logistic fit (as described by Bowen and Jerman, *TiPS*, 1995, **16**, 413-417) to generate a concentration effect value. Antagonist Kb values were calculated using the equation:

$$Kb = IC50 / (1 + ([3] / EC50))$$

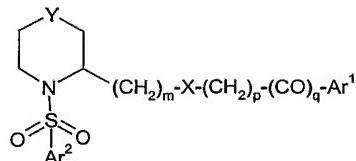
where EC50 was the potency of human orexin-A determined in the assay (in nM
10 terms) and IC50 is expressed in molar terms.

Compounds of Examples tested according to this method had pKb values in the range <6.4 to 7.6 at the human cloned orexin-2 receptor.

The application of which this description and claims forms part may be used as a
15 basis for priority in respect of any subsequent application. The claims of such subsequent application may be directed to any feature or combination of features described herein. They may take the form of product, composition, process, or use claims and may include, by way of example and without limitation the following claims:

CLAIMS

1. A compound of formula (I):



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(I)

wherein:

Y represents a bond, oxygen, NQ or a group $(\text{CH}_2)_n$, wherein n represents 1, 2 or 3; m represents 1, 2, or 3;

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p represents 0 or 1;

q represents 0 or 1 provided that when q = 1, p = 0.

X is NR, wherein R is H or $(\text{C}_{1-4})\text{alkyl}$;

Q is H or $(\text{C}_{1-4})\text{alkyl}$

Ar¹ is aryl, or a mono or bicyclic heteroaryl group containing up to 4 heteroatoms selected from N, O and S; any of which may be optionally substituted;

Ar² represents phenyl or a 5- or 6-membered heterocyclyl group containing up to 3 heteroatoms selected from N, O and S, wherein the phenyl or heterocyclyl group is substituted by R¹ and further optional substituents; or Ar² represents an optionally substituted bicyclic aromatic or bicyclic heteroaromatic group containing up to 4 heteroatoms selected from N, O and S;

R¹ represents hydrogen, optionally substituted $(\text{C}_{1-4})\text{alkoxy}$, halo, cyano, optionally substituted $(\text{C}_{1-6})\text{alkyl}$, optionally substituted phenyl, or an optionally substituted 5- or 6-membered heterocyclic ring containing up to 4 heteroatoms selected from N, O and S; or pharmaceutically acceptable salts thereof.

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2. A compound according to claim 1 where m is 1 when p is 0.

3. A compound according to claim 1 or 2 wherein X is NH.

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4. A compound according to claim 1 wherein when Ar¹ is aryl p is not 1.

5. A compound of formula (I) as defined in any one of Examples 1 to 23, or a pharmaceutically acceptable salt of any one thereof.

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6. A pharmaceutical composition comprising a compound of formula (I) as defined in any one of claims 1 to 5, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

7. Use of a compound of formula (I) as defined in any one of claims 1 to 5 in the manufacture of a medicament for the treatment of disorders where an antagonist of a human Orexin receptor is required.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 03/12406

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D401/12 C07D403/12 C07D405/12 A61K31/4523 A61P3/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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A	WO 02/44172 A (BRANCH CLIVE LESLIE ; JOHNSON CHRISTOPHER NORBERT (GB); SMITH ALEXANDE) 6 June 2002 (2002-06-06) page 2, line 26 - page 3, line 13; claim 1 -----	1-7
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 Further documents are listed in the continuation of box C. Patent family members are listed in annex.

° Special categories of cited documents :

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Date of the actual completion of the international search

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INTERNATIONAL SEARCH REPORT

International Application No

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